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Applicant	:	Daniel REDOULES, et al.
Serial N°.	:	09 / 937,673
Filed	:	September 28, 2001
Title	:	*BIOPRECURSORS OF A RETINOIC DERIVATIVE AND PHARMACEUTICAL AND/OR COSMETIC COMPOSITION*
Art unit	:	1623
Examiner	:	Devesh KHARE, Esq.

HONORABLE COMMISSIONER FOR PATENTS

ALEXANDRIA, VA 22313

DECLARATION UNDER 37 CFR § 1.132

I, Daniel REDOULES, a citizen of France, 42 avenue Etienne Billières 31300 TOULOUSE, FRANCE, do hereby state and declare that :

I hold a degree of Ph.D chemistry from Toulouse University in 1999.
I started to work in 1990 as researcher at PIERRE FABRE RESEARCH INSTITUTE.
Since 1994, I have been working as the Head of the skin chemistry Laboratory at PIERRE FABRE RESEARCH INSTITUTE (resume attached herewith).

* * * * *

1) The over expressed β-glucocerebrosidase ability to recognize substrates other than its natural substrate has been studied.

For this study, gluco-conjugates have been synthesized and the β-glucocerebrosidase ability to hydrolyze said gluco-conjugates has been observed.

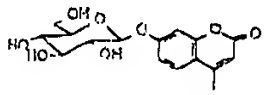
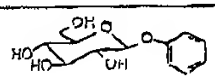
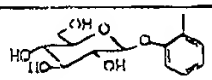
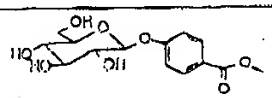
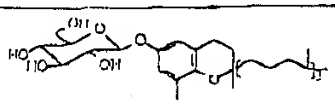
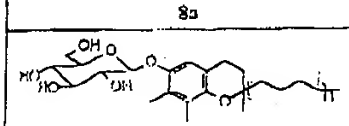
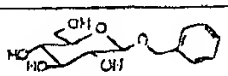
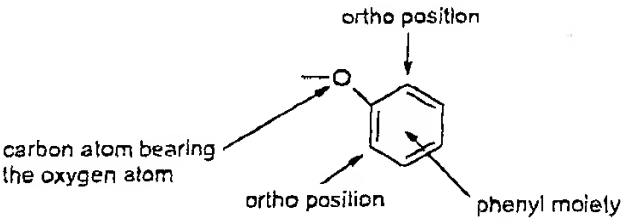
Structure	Released molecule	K_M (mM^{-1})	V_M ($nmol.hour^{-1}.mg^{-1}$)
 4-methylumbelliferyl-glucopyranoside	4-methylumbelliferone	7.2 ± 0.8	9300 ± 650
 3a	Phenol	> 30 mM	no mesure available
 4a	2-methyl-phenol		No hydrolysis
 6a	4-hydroxy-methyle benzoate	19.8 ± 4.9	1983 ± 363
 8a	δ-tocopherol	$7.10^{-3} \pm 1.10^{-3}$	453 ± 20
 9a	γ-tocopherol		No hydrolysis
 12a	benzyle		No hydrolysis

TABLE 1: Constants (K_M et V_M) of the synthesized gluco-conjugates corresponding to their hydrolysis by over expressed β-glucocerebrosidase.

Results given in Table 1 illustrate:

- the necessity to associate with a glucose unit a good leaving group (most of the studied phenolic derivatives are good leaving groups);

- the necessity to avoid a steric hindrance at the "cut-off" site. For example, molecules having on the phenyl moiety a methyl group at the ortho position relative to the carbon atom bearing the oxygen atom, which is linked to the C_1 atom of the glucose unit, are not hydrolyzed;



- the necessity to have a lipophilic glucose conjugated unit.

2) Furthermore, the transcutaneous diffusion and the metabolism in skin of arbutin retinoate have been studied. The results of this study demonstrate that the retinoic acid is released in situ (see figures 1 and 2, annex 2).

Figure 1 shows the arbutine retinoate metabolism into hydroquinone retinoate then into retinoic acid.

Figure 2 shows the repartition of retinoic acid in cutaneous compartment.

Experiments conditions: a 0.2 % arbutin gel is applied on human tissue epidermis, which are restored and maintained alive. They have all the features of differentiated and mature skin (barrier rule and active metabolism).

The mechanism of the compounds according to the invention is as follows:

- due to its amphiphilic structure, the gluco-conjugate penetrates through the skin by passive diffusion;
- then, on the one hand, the glucose unit, i.e. an hydrating agent, is released and, on the other hand, the ester form with the spacer group and the active agent is also released;
- the spacer group (which may also have a pharmaceutical and/or cosmetic activity, e.g. hydroquinone is a depigmenting agent) and the retinoic acid are released close to the targeted cells.

* * * * *

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 or the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant saith not.

Signed Toulouse on January 19, 2004

Postal Address: 42 avenue Etienne Billières 31300 Toulouse

Attachment hereto : - Resume.

- Figures 1 and 2.

ANNEX 1

Daniel REDOULES

9, rue Adolphe Coll
31300 TOULOUSE
FRANCE
Born on May 09, 1964

DIPLOMA

1990: Master degree in Chemistry from Toulouse University.
1999: PhD in Chemistry from Toulouse University.

INDUSTRY

1990– 2004: Head of the skin chemistry Laboratory for studies of skin physiopathologiy.
Principal Objectives:
1. Define pharmacological targets,
2. Conceive new cosmetic and dermatological active ingredients,
3. Evaluate active ingredients with clinical studies

PUBLICATIONS

Around 10 publications in reference journals

Inventor in 4 patens dealing meanly with bioprecursors of active compounds.

ANNEX 2

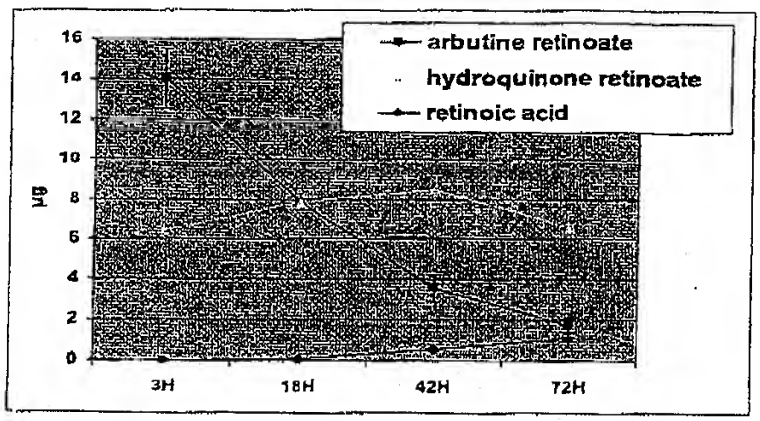
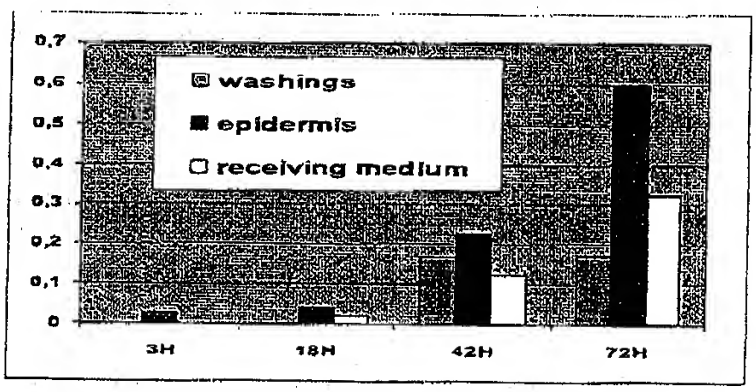


Figure 1



- **At 3H : apparition of a retinoic acid in epidermis**
- **At 18H : diffusion in receiving medium**
- **At 42H : high quantity in epidermis and receiving medium + backscattering to the surface**
- **At 72 H: high quantity in epidermis and receiving medium**

Figure 2